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Histogenesis of Exocrine Pancreatic Cancer in the Hamster Model

by Parviz M. Pour*

There is strong evidence that induced pancreatic adenomas and carcinomas derive from ductal and ductular cells in the pancreas. We base our beliefs on our knowledge of the embryology and histology of the pancreas in Syrian golden hamsters, along with the sequential alterations that occur during exocrine pancreatic tumor formation. This concept also has been supported by much experimental evidence, including autoradiographic, immunologic and *in vitro* studies. We also present other viewpoints on the origin of pancreatic cancer histogenesis and outline certain areas of disagreement. We report the development of acinar cell lesions under certain experimental dietary conditions in hamsters (the lesions resemble those commonly seen in the rat pancreatic tumor model) and the nature of these lesions.

Although the Syrian golden hamster model developed at the Eppley Institute (*1–3*) has been accepted generally as the best means to study pancreatic carcinogenesis, confusion has arisen because of differing concepts concerning the histogenesis of the induced lesions. There are three main points of view with regard to this element of the model. One group of investigators believes pancreatic lesions [at least those induced by *N*-nitrosobis(2-hydroxypropyl)amine or BHP] derive from acinar cells that undergo ductlike dedifferentiation during carcinogenesis (*4,5*). Another group has the distinct view that all induced lesions in hamsters derive from ductal and ductular cells (*2,3,6,7*). The third group embraces both of the foregoing theories (*8,9*). However, all three agree that the final stage of tumor development is of a duct (ductular) cell type.

The present study focuses on the histogenesis of pancreatic tumors in the hamster model and discusses some of the basic problems and arguments relative to the concept of pancreatic tumor cell origin. The presentation also includes some data on modification of carcinogenesis by diet.

Studies in tumor histogenesis preclude knowledge of certain basic principles of the particular tissue, especially with regard to embryology and histology. The embryology of the hamster pancreas has not been as extensively studied as has that of the human pancreas.

However, although data are fragmentary, the morphogenesis and ontogenesis of the hamster pancreas have

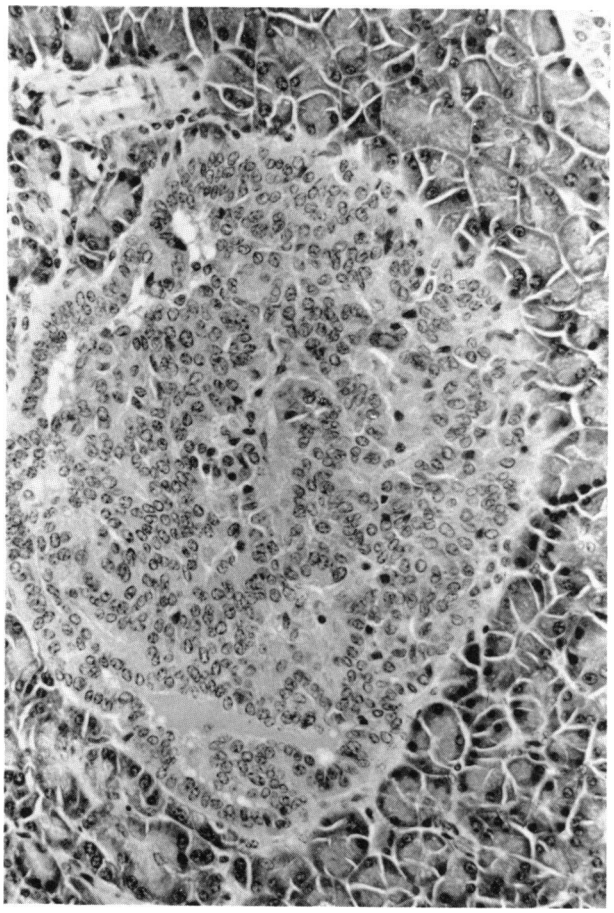

FIGURE 1. Secretion-containing space (ductule) in the periphery of an islet in a Syrian hamster. H & E, ×195.

*The Eppley Institute for Research in Cancer and Department of Pathology and Laboratory Medicine, University of Nebraska Medical Center, Omaha, NE 68105.

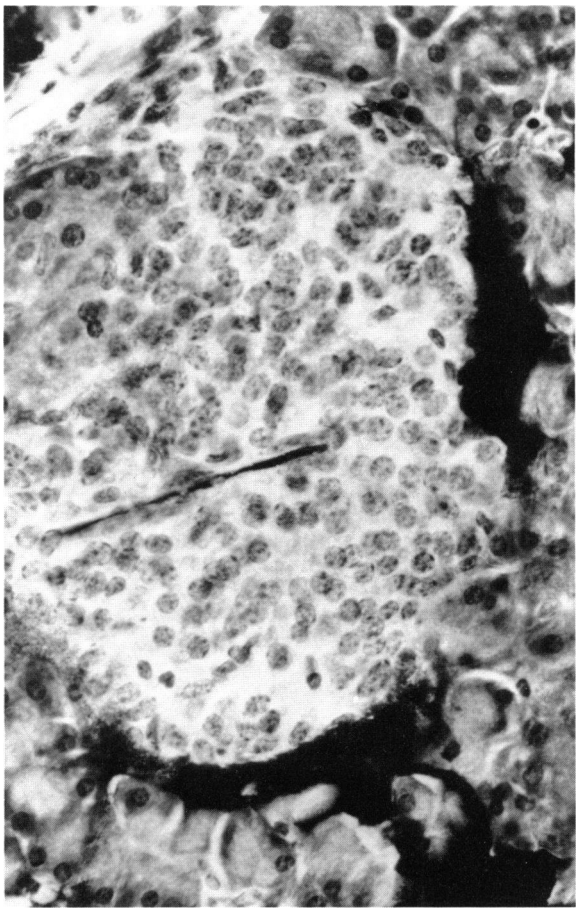

FIGURE 2. Demonstration of peri-insular and intra-insular (center) ductules by India ink. H & E, ×195.

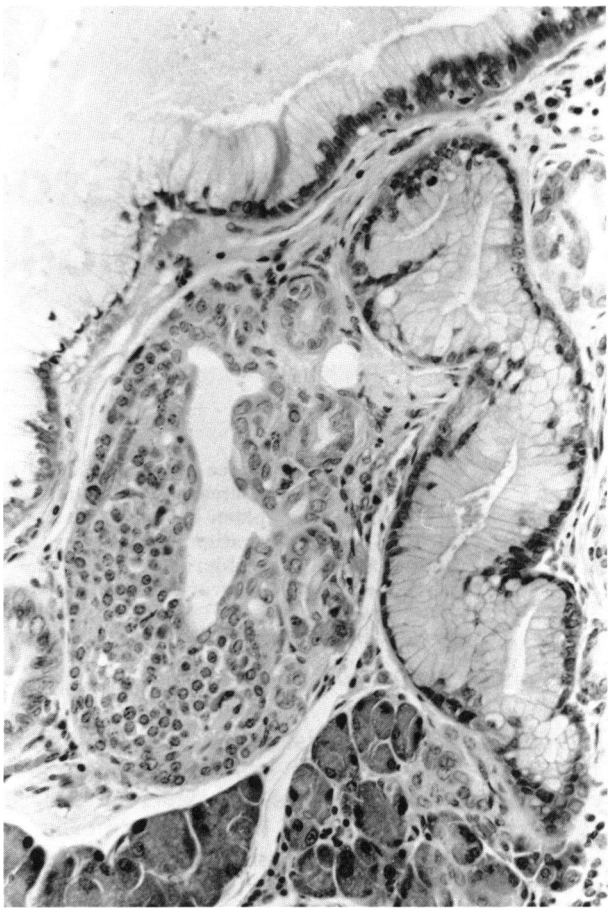

FIGURE 3. Pyloric cell type metaplasia of a large (top) and smaller duct (right). Note the intra-insular ductular complex (middle). H & E, ×195.

been found to be similar to that in humans, except that organ development in hamsters is considerably more rapid (*10–12*). The embryogenetic period for hamsters is about 36 hr, and organogenesis of the pancreas in this species occurs between days 11 and 15 of gestation. This explosive development makes it difficult to follow the sequential formation of organ architecture. However, available data indicate that, as in humans, the embryonic pancreas begins with branching tubules or ductules, from which islet and later, acinar cells derive. Consequently, it is reasonable to consider these ductular or tubular cells the foundation or stem cells of the pancreas. Also, as in humans, ductal and endocrine tissue remain closely associated during the life span of the animals (*3*). Many islets in the hamster pancreas are surrounded (peri-insular) or traversed by (intra-insular) ductules. The presence of intra-insular ductules was first described in 1911 in the guinea pig by Bensley (*13*), who, via meticulous staining procedures, observed that some ductules penetrate into the islet and are lined with a mixture of mucinous and islet cells.

Certain islets in hamsters are limited in the periphery by secretion-containing channels (Fig. 1) lined with cells that are almost indistinguishable from the adjacent islet cells. Often, however, these peri-insular channels are tiny and nearly invisible. They can best be demonstrated by injecting India ink into the pancreatic ducts (Fig. 2). We have reason to believe that the cells of the peri-insular ductules are not only part of the excretory channels for the exocrine pancreas, but are also the foundation for islet cells, as are other ductular cells, including centroacinar cells (*3*). The ability of the centroacinar cells to produce islet cells is not unique to hamsters and has been found in many species, including humans (*3*). There are no other pancreatic cells with this ability, and there is evidence that the ductular cells and centroacinar cells are the most responsive units of the ductal system (*2,3,14*), based on their enormous potential to display a wide spectrum of phenotypic expression, including various forms of metaplastic change (Figs. 3–8). Formation of glycogen-containing cells (Fig. 6) is evidence of the origin of the various metaplastic cells from the terminal ductules and from centroacinar cells, because embryologically these cells

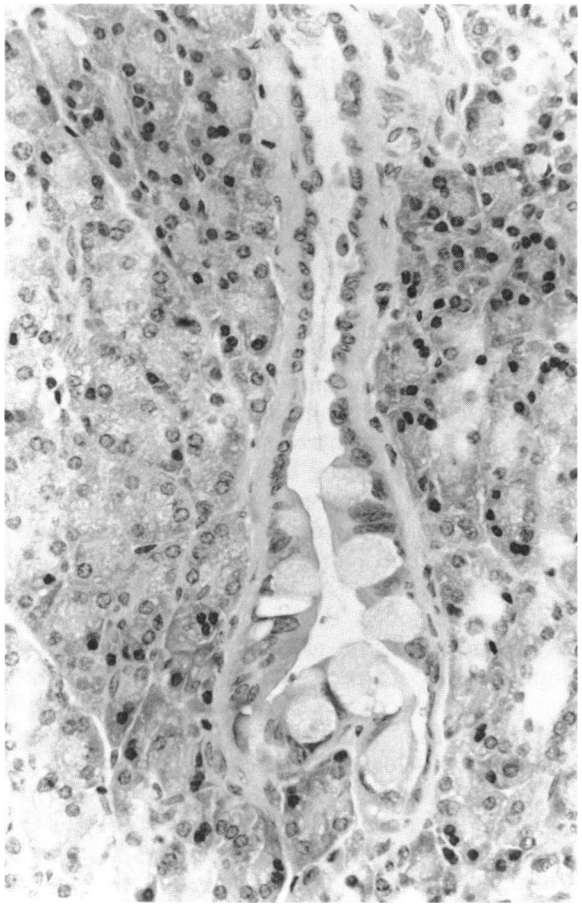

FIGURE 4. Goblet cell metaplasia in a pancreatic duct. H & E, ×195.

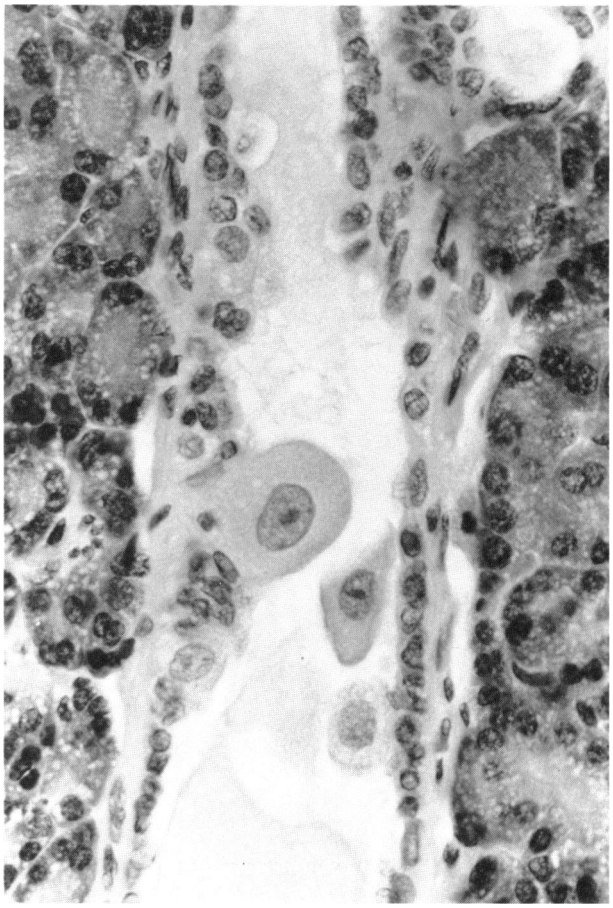

FIGURE 5. Eosinophilic (oncocytic) cell metaplasia at different stages of development from a pancreatic duct. H & E, ×390.

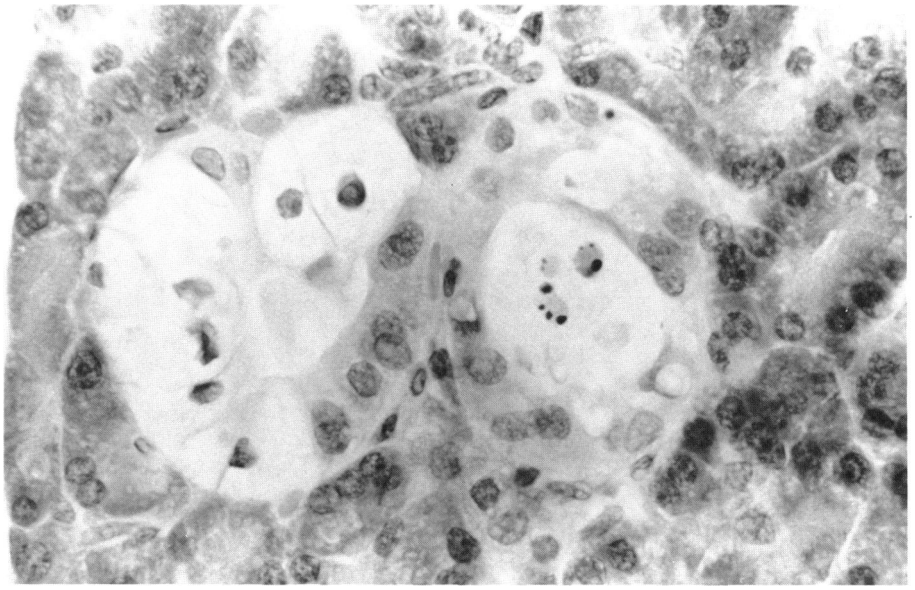

FIGURE 6. Eosinophilic and clear (glycogen-containing) cells arising from pancreatic terminal ductules [see also Fig. 4.82 by Pour and Wilson (*3*)]. Note remnant of an acinus at lower left corner. H & E, ×390.

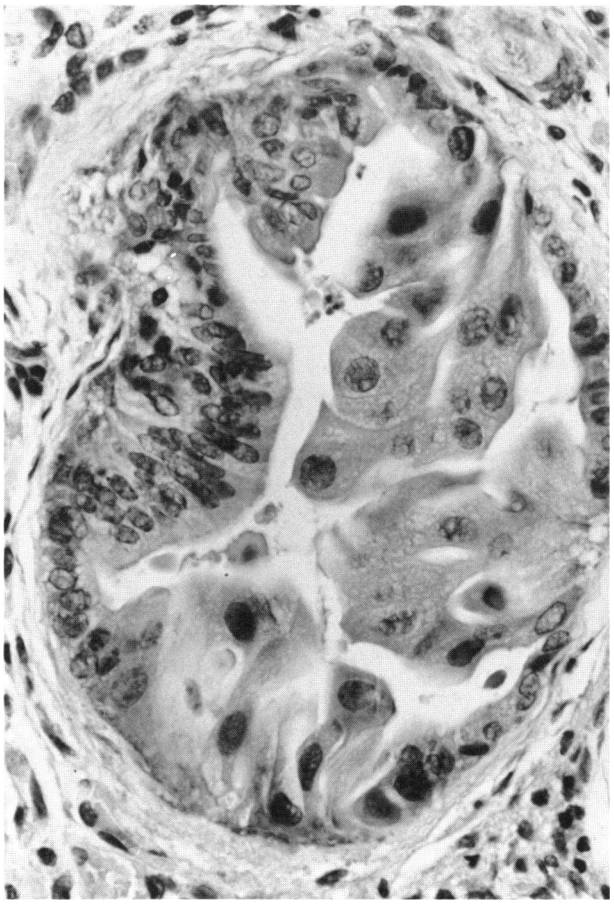

FIGURE 7. Atypical eosinophilic cells protruding into the lumen of a pancreatic duct, partially covered with multi-layered cylindric cells. H & E, ×390.

alone have been found to form and to store glycogen (*15*). Since according to our findings, the centroacinar cells are important in pancreatic tumor formation, a brief description of their known relationship with acinar cells may allow us to understand the existing problems in interpreting processes that occur during neogenesis.

The canal system of the pancreas consists of main or type 1 ducts and secondary type 2 ducts, which (contrary to the situation in other glands) merge without intermediary ducts into long connecting or interlobular ductules (*16*). These ductules in turn merge into terminal buds formed by centroacinar cells, which later give rise to acinar cells. The relationship between acinar and centroacinar cells is complex. In the mature organ, the acini form individual glandular units, the monomers, in which centroacinar cells usually line the small canaliculi connected to each monomers (Fig. 9). Consequently, the term centroacinar cell in these acini (monomers) may be incorrect, since the cells are not located within them. During development of acini from terminal buds, the latter multiply by either forming new buds or through division of existing acini (*16*). Since acini formation ends at different stages of development, a peculiar centroacinar–acinar complex, termed polymers, develops. In these polymers a large proportion of the "still open" glands are formed by centroacinar cells located apically to or between acinar cells (Fig. 10).

This brief introduction concerning the relationship between the exocrine and endocrine pancreas will hopefully lead to an understanding of the complicated events surrounding pancreatic tumor development. To demonstrate tumor histogenesis, we have collected data from animals exposed to the carcinogen only once, since

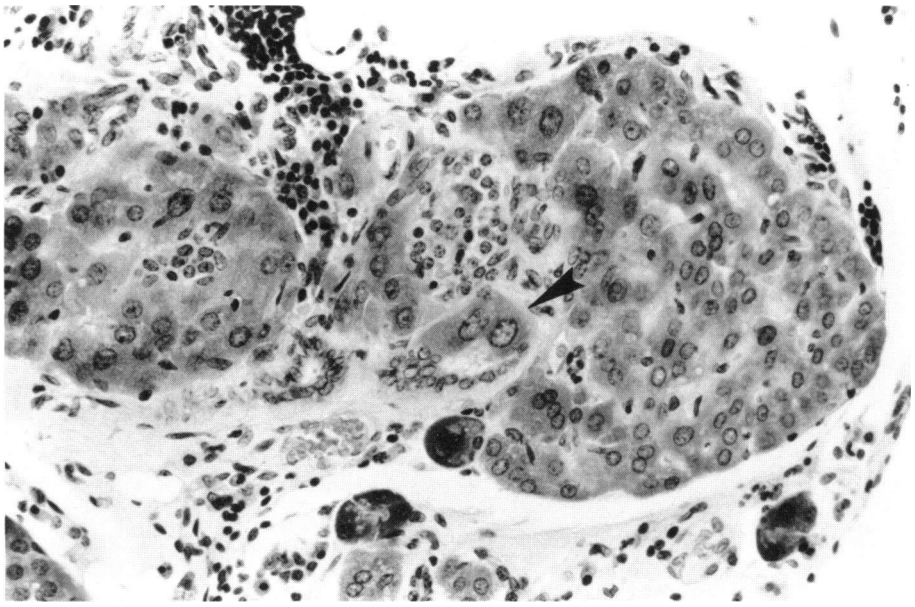

FIGURE 8. An atrophic pancreatic area depicting hepatocytelike cells surrounding islets (left and middle) and populating a ductule (arrowhead).

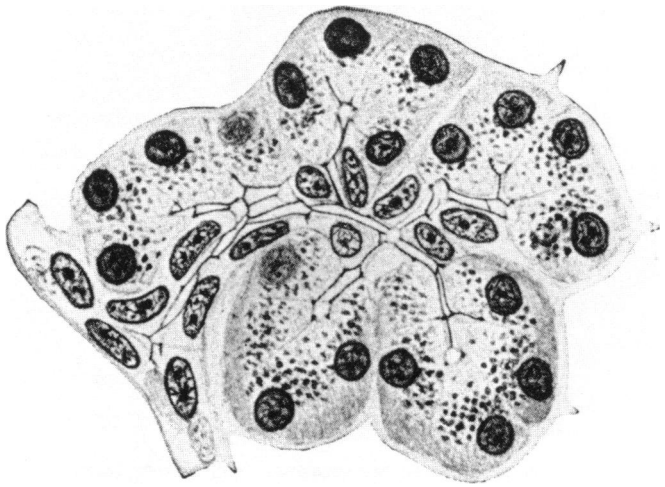

FIGURE 9. Pancreatic terminal ductular cells merging into centroacinar cells, which line interacini canaliculi, without extending into the acini lumen. Each acinar gland presents a monomer. From v. Möllendorff (*16*).

by this treatment scheme the neoplastic event represents a slower, easier-to-follow stepwise process. This is in contrast to alterations found in animals that had been treated repeatedly (*5,17*). Repeated applications of high doses of nonspecific carcinogens, such as *N*-nitrosobis-(2-hydroxypropyl)amine (BHP), create serious problems, because toxic and carcinogenic processes go hand-in-hand with regenerative and neoplastic events. Therefore, in our opinion, single, low and nontoxic doses of carcinogens, such as *N*-nitrosobis(2-oxopropyl)amine (BOP), which have an almost selective effect on the pancreas, are the most reliable means to investigate tumor histogenesis. By this method of dosing, initial and visible morphologic alterations begin weeks after carcinogen treatment. For example, we may see such changes 12 weeks after a dose of 20 mg/kg and 32 weeks after a dose of 10 mg/kg of this carcinogen. At these times the acute toxic effects of the compound have subsided, and therefore changes observed after this time could express the neoplastic effects of the carcinogen.

Degeneration and necrosis in an acinar cell group (monomer or polymer) are the first alterations and appear a few weeks after a single carcinogen injection (Fig. 11). This particular type of acinar cell necrosis has been found to be due to a marked hypertrophy and hyperplasia of centroacinar and intercalated cells (Figs. 11 and 12) and results in blockage of the secretory channels of affected acini. The affected acinar cells then become necrotic and are gradually replaced by proliferating terminal ductular and centroacinar cells (Figs.

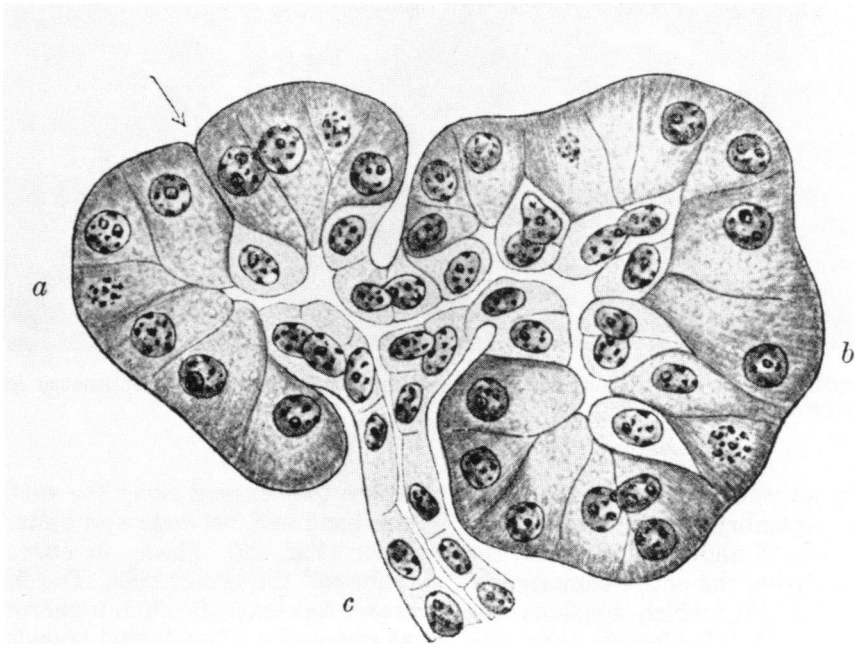

FIGURE 10. Terminal branching of a pancreatic ductule (c) in acini of diameric (a) and polymeric (b) nature. The centroacinar cells line the surface of incompletely developed acini. The connective tissue between two incompletely separated acinar cell complexes (arrow) reaches the centroacinar cell. From v. Möllendorff (*16*).

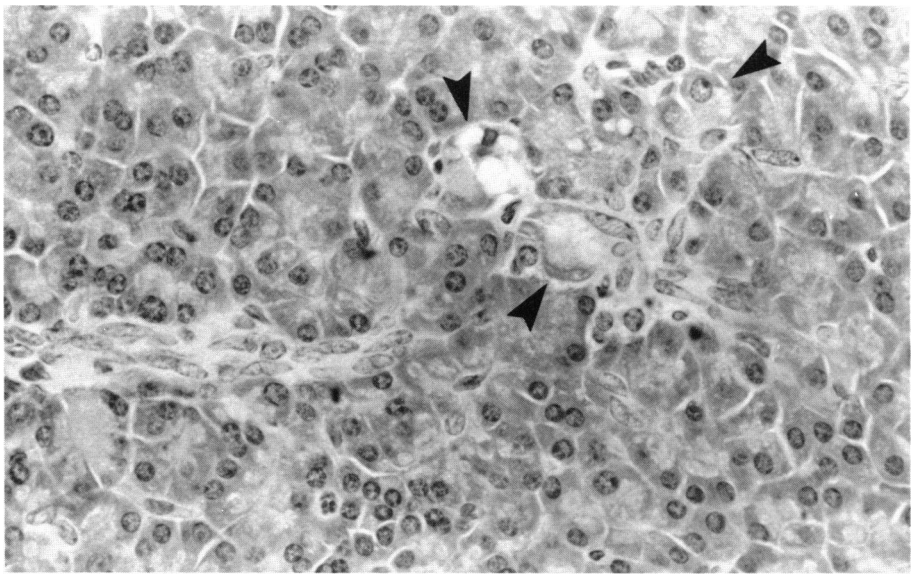

FIGURE 11. Degeneration of acini (arrowheads), and hypertrophy and proliferation of ductular (centroacinar) cells. Note marked cell enlargement of an interlobular ductular cells (left middle). H & E, ×195.

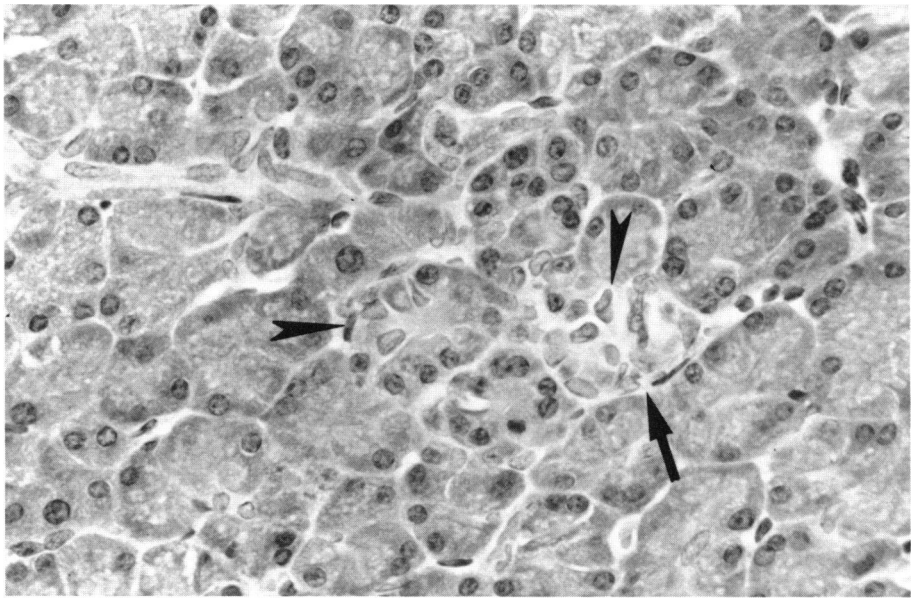

FIGURE 12. Hypertrophy and hyperplasia of interlobular (left upper part) and terminal ductular and centroacinar cells (arrowheads), partially replacing an entire acinus (arrow). H & E, ×195

13–15). These ductular, as well as ductal cells, then begin to form (by repeating embryological development processes) islet cells (Figs. 16 and 17) and retain the ability to form islet cells during the entire tumorigenesis process (Figs. 18 and 19), which explains the occurrence of mixed insular-ductular lesions (Fig. 19), to be described later.

Another remarkable process also occurs at this time. The centroacinar cells, which are usually polygonal or spindle-shaped, become elongated and form long processes that extend along the surface of acinar cells on one hand and between and under acinar cells, on the other (Fig. 20). These, in effect, nearly strangle or "squeeze" the acinar cells. The formation of such processes has been shown in numerous other tissues to be an expression of malignant transformation. Since these processes are extremely tiny, they can be seen only by electron microscopy (Fig. 20), as has also been demonstrated by Flaks and his colleagues (*17*). After application of a ductal-specific antigen, they are found as a

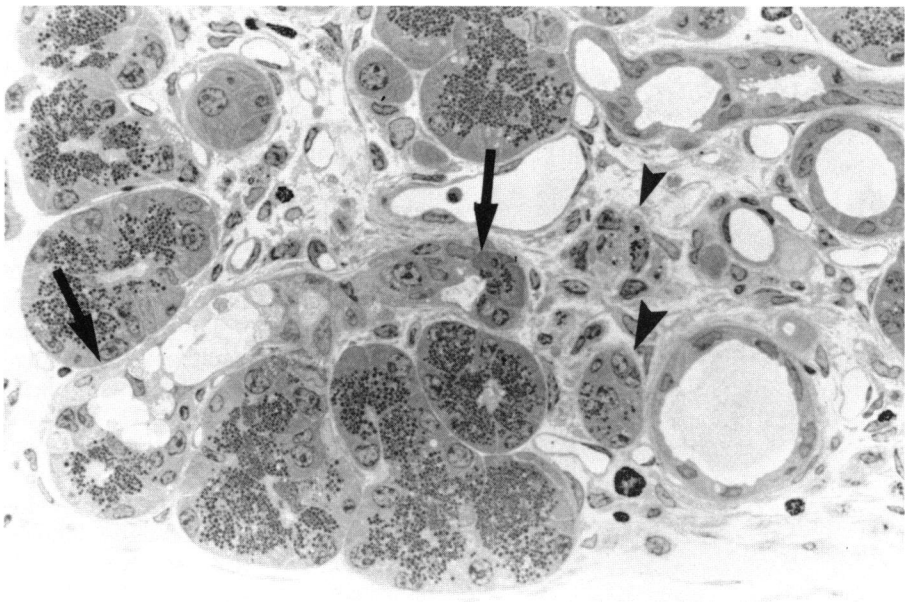

FIGURE 13. Degenerated acini (arrowheads) and their replacement by proliferated ductular cells (arrows). Note that ductular cells grow into the acini from the terminal ductular sites. Epon, Giemsa, ×195.

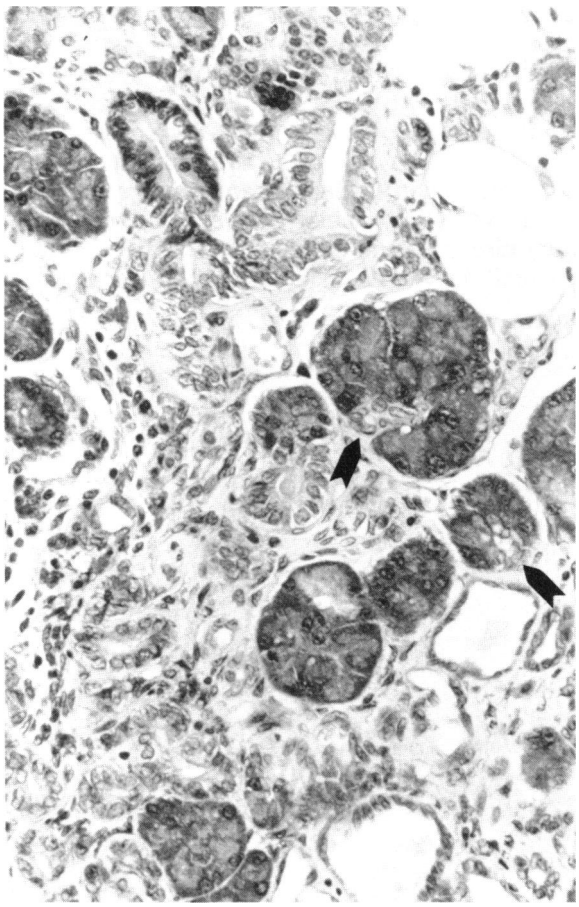

FIGURE 14. Multifocal proliferation of pancreatic ductular cells partially or completely replacing acini. Note hyperplastic terminal ductular cells (arrowheads).

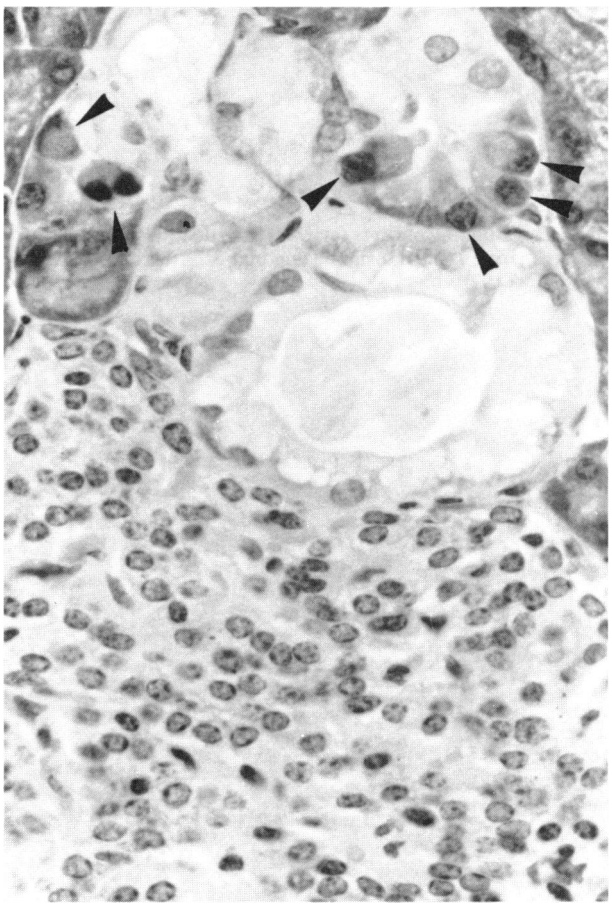

FIGURE 15. Degeneration of peri-insular acinar cells (arrowheads) and their replacement by ductular cells of various cytological types. H & E, ×390.

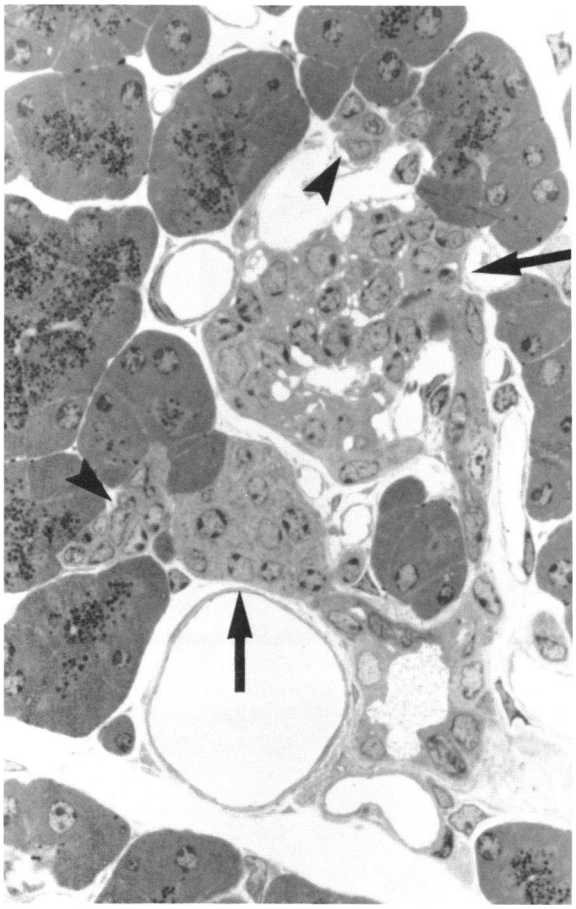

FIGURE 16. Budding of islets (arrows) from ductules. Note hypertrophy and hyperplasia of terminal ductular cells (arrowheads). Epon, Giemsa, ×195.

narrow rim on the surface of the acinar cells; under light microscopy, they give the impression that the positive reaction occurs at the luminal surface of the acinar cells, and this may be considered evidence of the beginning of dedifferentiation of acinar cells to ductular cells. I believe this complex process to be the major area of confusion in interpreting carcinogenic events by some investigators.

The acinar cells surrounded by these atypical centroacinar cells, suffocate, die and are expelled into the lumen. Some may be phagocytized as indicated by Moore et al. (7). They are then gradually replaced by elongated centroacinar cells (Figs. 11–14) which form pseudoductules or tubular complexes (Fig. 14), some of a malignant type (Fig. 21). We have no argument as to the constituency of these tubular structures, but we are convinced they represent atypical ductular (centroacinar) cells and imitate embryonic tissue rather than dedifferentiated acinar cells. These ductular and tubular cells, like the embryonic and stem cells of the pancreas, clearly can differentiate, upon certain stimuli, toward insular cells, acinar (or acinarlike) cells or toward both (Figs. 22 and 23). The occasional gradual formation of acinar cells, with all the intermediary cells from the ductular cells, should not be confused with the process of gradual dedifferentiation of acinar cells to ductular cells. The differing philosophies relative to formation of these tubules are due to the direction from which we see them develop. We believe development of acinar or acinarlike cells to be the endpoint of ductular cell differentiation, whereas another group has the opposite view—that acinar cells are the starting point and ductular cells the endpoint

Concomitantly with pseudoductular formation, we

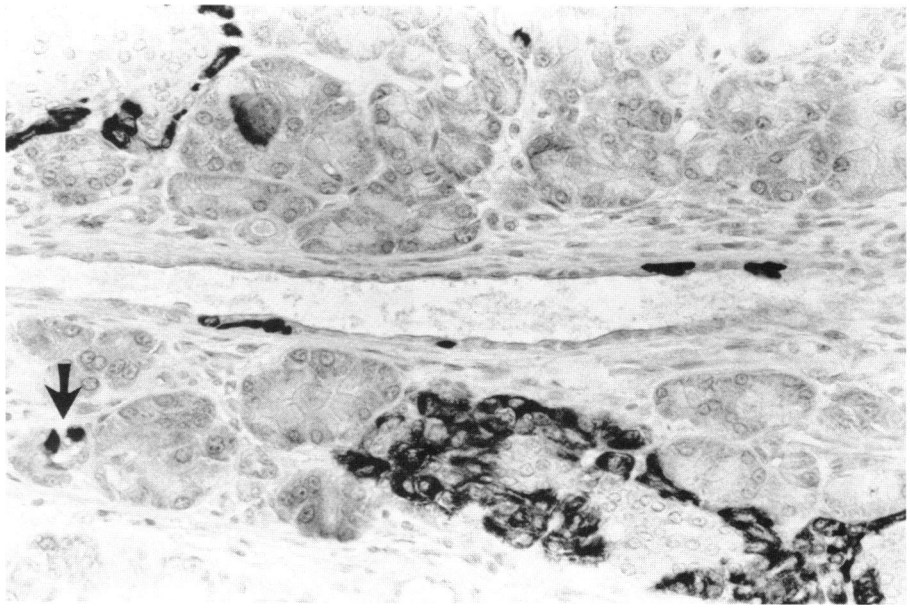

FIGURE 17. Glucagon-producing cells (black) in the wall of a large duct (middle), in the periphery of two islets (upper left and lower right), and within the epithelium of a terminal ductule (arrow). Remarkable increase of these glucagon-containing cells in the lower right islet. Immunoperoxidase–antioxidase with antiglucagon. ×195.

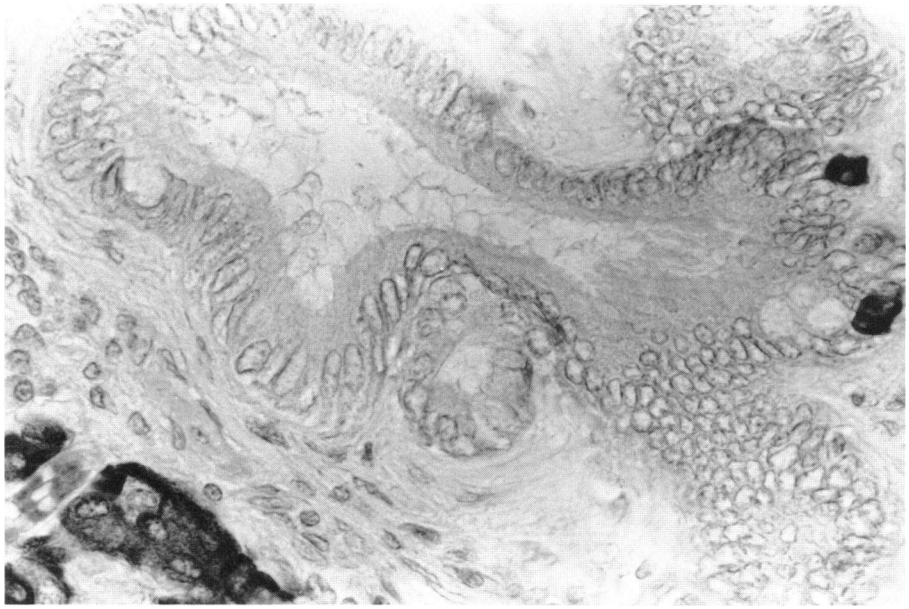

FIGURE 18. Glucagon-containing cells (black) in the wall of a hyperplastic pancreatic duct. Part of an islet is at lower left corner. Immunoperoxidase–antiperoxidase with antiglucagon. ×390.

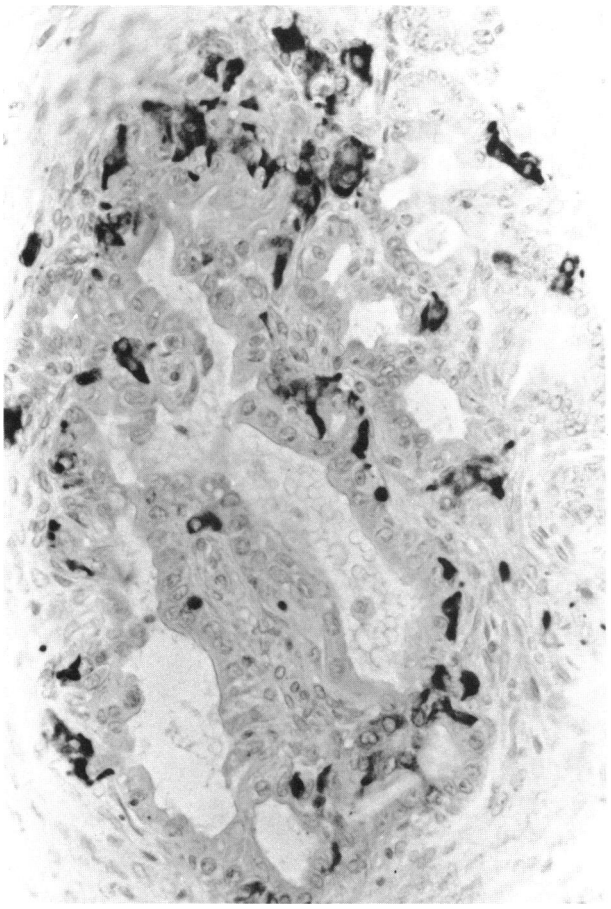

FIGURE 19. Mixture of ductular and insular (glucagon containing) cells in an early ductular carcinoma. Immunoperoxidase–antiperoxidase with antiglucagon. ×195.

find islet cells (nesidioblastosis) to develop from either hyperplastic ductules, as several islet cell buds (Fig. 16), or from the centroacinar cells. As stated previously, the ability of ductal, ductular and centroacinar cells to form islet cells is retained in their malignant counterparts (Fig. 19). The latter characteristic can be demonstrated by the immunoperoxidase–antiperoxidase method, which reveals the presence of different islet cells, including alpha, beta and somatostatin cells, in the base of malignant epithelium. Interestingly, the potential for malignant epithelium to form islet cells was recently clearly demonstrated in other species (*18*), including man (*19–21*), and not only in cases of primary pancreatic cancer, but also in their metastases. The latter finding clearly indicates that these islet cells are an integral part of the neoplasms.

Another process observed during carcinogenesis is peri-insular and intra-insular ductule proliferation. These ductules, initially obscure in untreated hamsters, become prominent and begin to proliferate (Fig. 24), and the cells lining them are either similar to ductular cells or remarkably similar or identical to immature islet cells—the so-called islet cell precursors (*3*). At this stage, we find a mixed islet and ductular cell population under electron microscopy (*3*) and by the immunoperoxidase technique (Fig. 25). In a more advanced carcinogenic process, intra-insular ductules increase in size and gradually occupy the entire islet. This event results in formation of structures consistent with microcystic or papillary cystic adenomas. In other instances, however, the intra-insular ductules display progressive hyperplasia, often with increased mitotic figures (Figs. 26 and 27), and ultimately become invasive. In some instances, ductular and insular cell

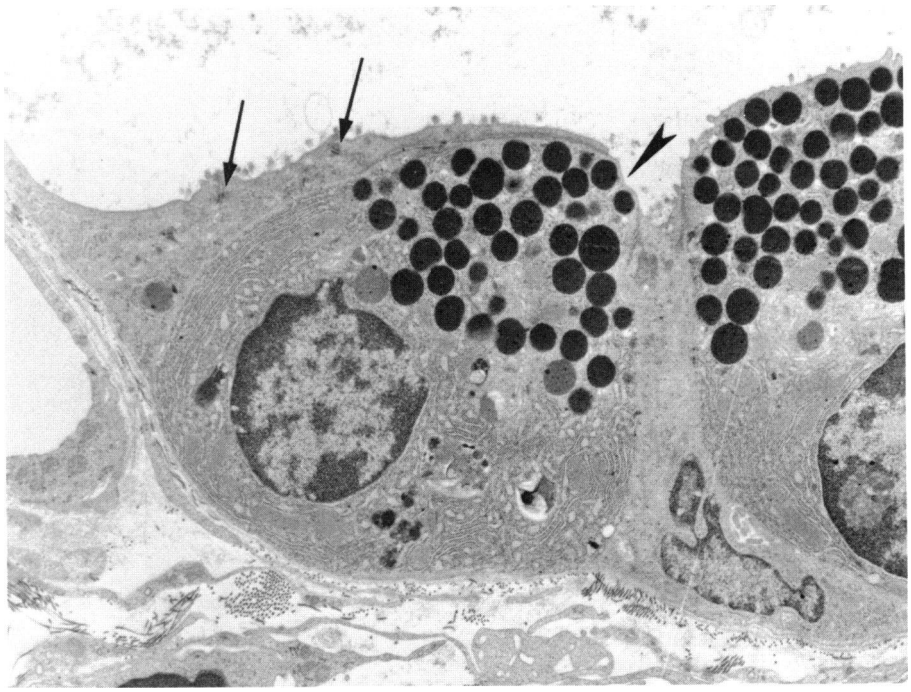

FIGURE 20. Long processes of centroacinar cells connected by desmosomes (arrows) cover the major portion of an acinar cell in which zymogen granules are directed toward the remaining small luminal surface (arrowhead). Part of another (centroacinar) cell is seen between the two acinar cells. ×8900. [See also Fig. 4.55 of Pour and Wilson (*3*) and Fig. 8 of Flaks et al. (*17*)]

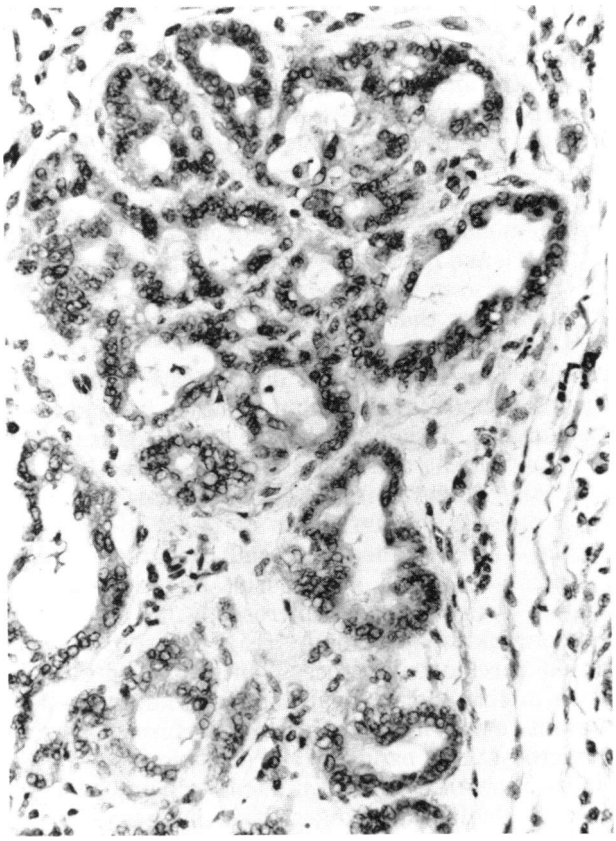

FIGURE 21. Pseudoductular complex composed of irregular, small glandlike structures lined with pleomorphic cells, consistent with the term ductular *ca in situ*. H & E, ×320.

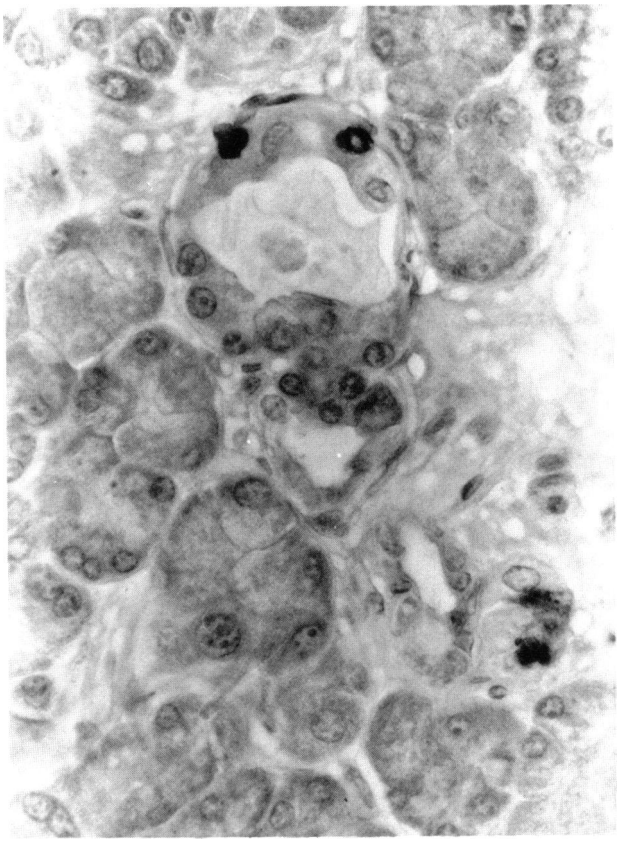

FIGURE 22. A pseudoductule lined by acinarlike cells with interspersed glucagon-containing cells (black). See also Fig. 23. Immunoperoxidase–antiperoxidase with antiglucagon. ×390.

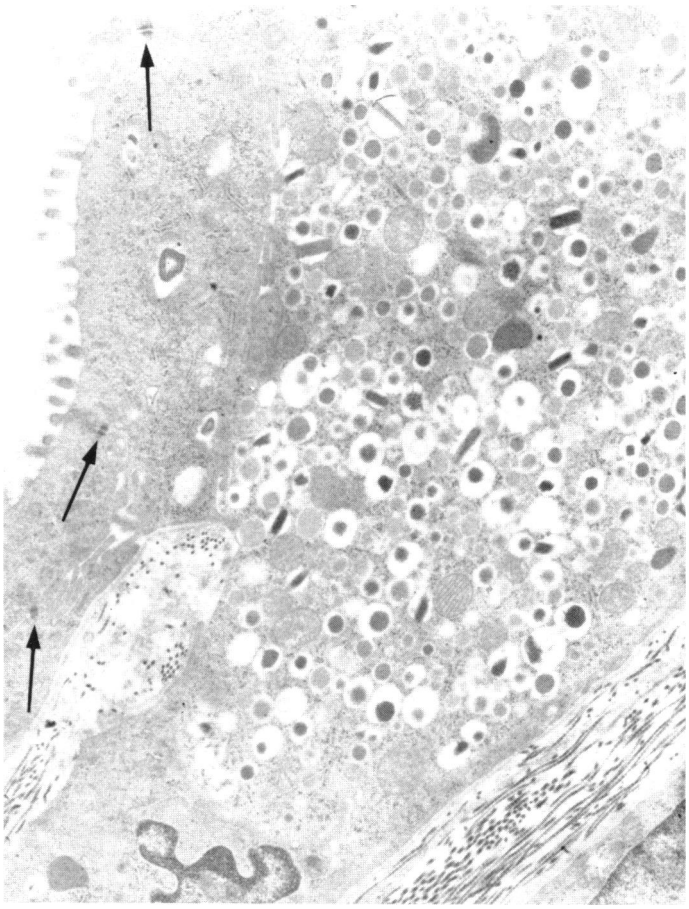

FIGURE 23. A B-cell between several ductular cells, connected by desmosomes (arrows), in a pseudoductule, like that in Fig. 22. ×19,150.

elements proliferate simultaneously and result in neoplasms consistent with mixed insular-ductular tumors (Fig. 19), as has also been described in man (*3*).

There is yet additional evidence for the ductal/ductular cells as tumor progenitor cells. Autoradiographic examination during pancreatic carcinogenesis demonstrates (*22*) increased thymidine incorporation predominantly in ductal and ductular cells (Fig. 28).

Nine percent of recipient hamsters bearing transplanted BOP-induced pancreatic tumors developed a highly specific ductulitis that also involved intra-insular ductules (*23*). Since tumors often are known to retain some antigenic determinants of their tissue of derivation, we assumed the transplanted tumor in the subcutaneous region of the animals had elicited an immune response to antigenic determinants present on the surface of tumor cells, derived from ductular cells. This antibody could cross-react with the antigen present on the normal pancreatic ductular cells. Immunohistochemical examination of pancreases with pancreatic ductulitis revealed a specific reaction of ductules to hamster anti-IgG raised in rabbits (*22*).

We have found a specific antigen produced by BOP-induced pancreatic tumors (*22,24*) that is present in all induced premalignant and malignant lesions, but not in normal tissue (Fig. 29). An immunohistochemical study using peroxidase–antiperoxidase techniques revealed selective staining of hyperplastic ductal, ductular and centroacinar cells, but not of other cell components (Fig. 30).

We have postulated that the effect of streptozotocin (SZ) and BOP on the pancreas is similar in that both are methylating agents and affect the ductular cells (*25*). Evidence for a role of ductular cells as the target for SZ derives from the observation in many species, including the hamster, that islet cell tumors induced by SZ derive from ductular cells (*26,27*). We assumed differences in the quantity or quality of DNA alkylation determine the direction of ductular cell differentiation, either to insular cells (by SZ) or to ductular cells (by BOP). If so, combined treatment with SZ and BOP would result in potentiation of BOP carcinogenesis, and this was indeed the case (*25*). A significantly higher cancer incidence was found after SZ plus BOP than after BOP administration alone. Moreover, SZ alone induced a few ductular adenomas and ductal hyperplasia (*25*).

In vitro studies (unpublished) in isolated pancreatic cells demonstrated that ductal/ductular cells had: (a) a higher capacity to metabolize BOP, (b) a greater ability to form from BOP or *N*-nitrosomethylpropylamine

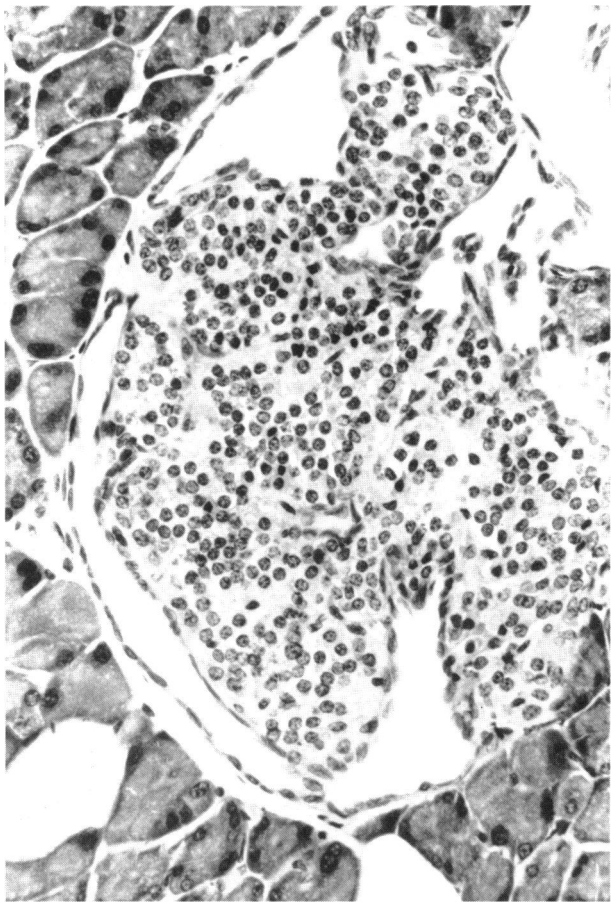

FIGURE 24. Proliferation of peri- and intra-insular ductules during early stages of pancreatic carcinogenesis. H & E, ×200.

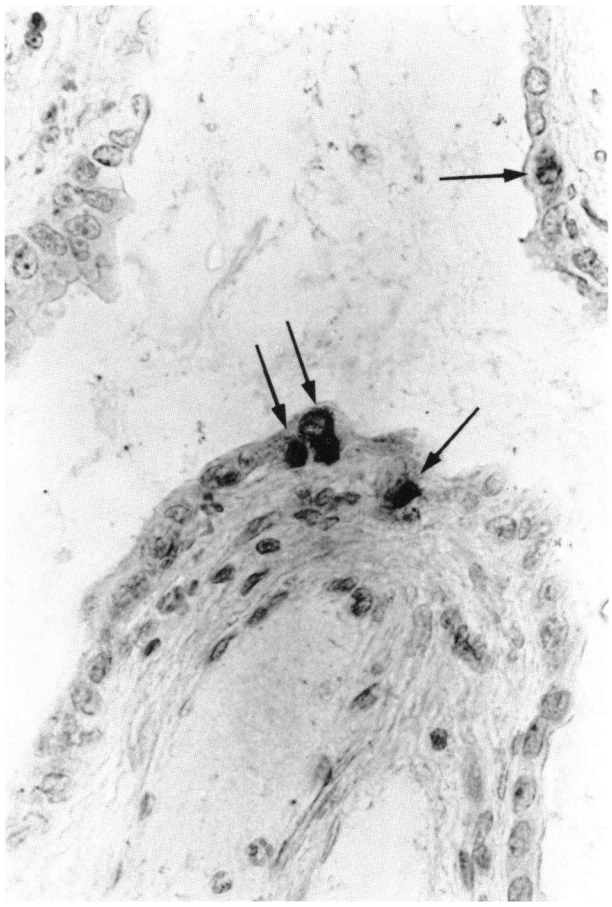

FIGURE 25. Four glucagon-containing cells (arrows) in the wall of a cystic ductular adenoma. Immunoperoxidase–antiperoxidase with antiglucagon. ×390.

(MOP), an assumed proximate carcinogen of BOP, (c) a greater accumulation of MOP and (d) a remarkably greater degree of DNA damage, when compared to other pancreatic cell components. Moreover, repair of DNA damage persisted in ductal/ductular cells, whereas it was rapidly repaired in acinar cells.

In summary, accumulating evidence indicates that ductal cells, but most especially ductular cells, are the progenitors of induced pancreatic tumors in hamsters. Recent data also support previous views that this is true for humans (*3,19–21*). Finally, recent experimental (*28*) and human data (*29*) suggest that even acinar cell lesions, termed hyperplastic foci or acinar cell nodules, derive from ductular cells. We could confirm this observation in individuals showing diffuse hyperplasia of centroacinar cells and nesidioblastosis (unpublished). This phenomenon has also been seen in experiments utilizing certain dietary regimens (*30,31*).

Induction of acinar cell lesions brings us to other problems we have faced in recent dietary studies. These include induction of a high incidence of acinar cell nodules in hamsters fed high fat diet (*30*), especially in BOP-treated hamsters. However, no clearcut data were seen relative to the relationship between level of fat and incidence and multiplicity of acinar cell nodules (*30*). The lesions were also present in animals given low fat diet and were more numerous in those receiving medium fat diet. In the latter, the lesions occurred in a higher incidence in females and in a greater multiplicity in males (*30*). The cytologic appearance of some of the acinar cell lesions was consistent with malignancy in terms of nuclear shape and mitotic activity. However, there were no histologic criteria for the malignant nature of these well-defined lesions.

Later studies to examine the effect of dietary protein level in pancreatic carcinogenesis suggested the interaction between dietary fat and protein levels (and not the fat level *per se*) plays an important role in induction of acinar cell nodules, since medium levels of fat and protein had the greatest effect (*31*). Because acinar cell nodules were also found in non-BOP-treated hamsters, it was reasonable to believe that these lesions, at least in hamsters, reflect dietary adjustment and are of a reactive, rather than neoplastic, nature. Our recent

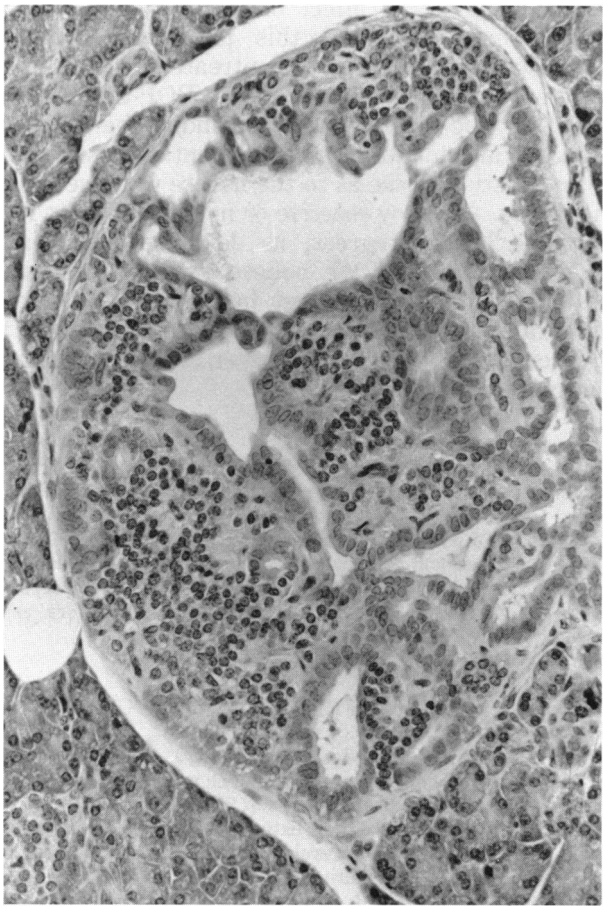

FIGURE 26. Hyperplastic peri- and intra-insular ductules which occupy nearly one-half of the islet. H & E, ×200.

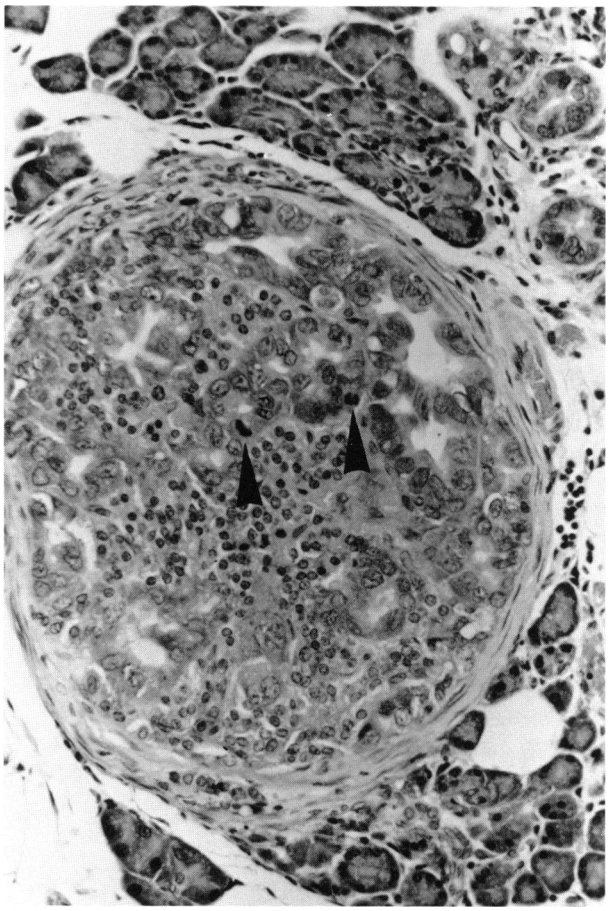

FIGURE 27. Malignant peri-insular and intra-insular ductular elements showing mitotic figures (arrowheads). H & E, ×195.

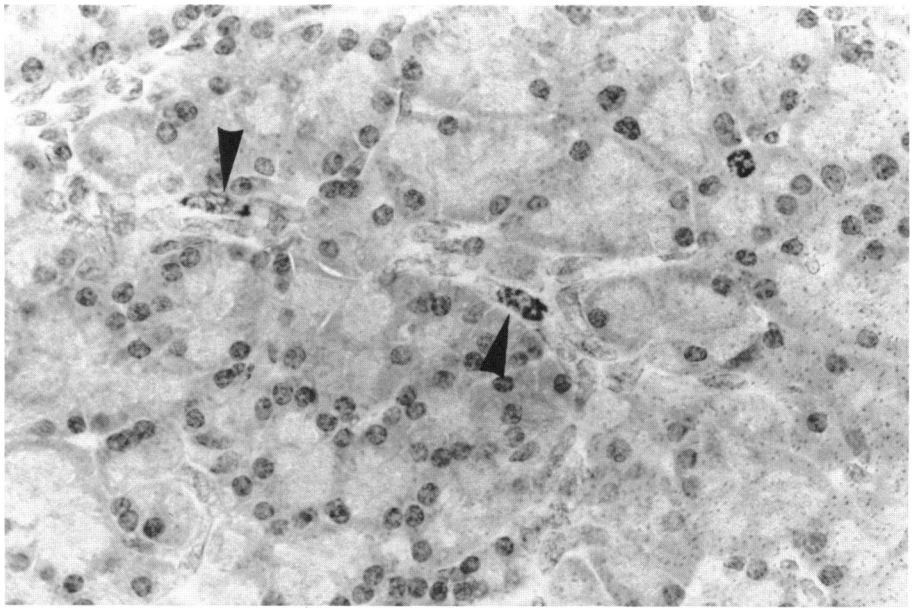

FIGURE 28. Early stage of pancreatic carinogenesis. Tritiated thymidine uptake by two interlobular ductular cells (arrows) and by one acinar cell (upper right). H & E, ×390. See also Pour et al. (*22*)

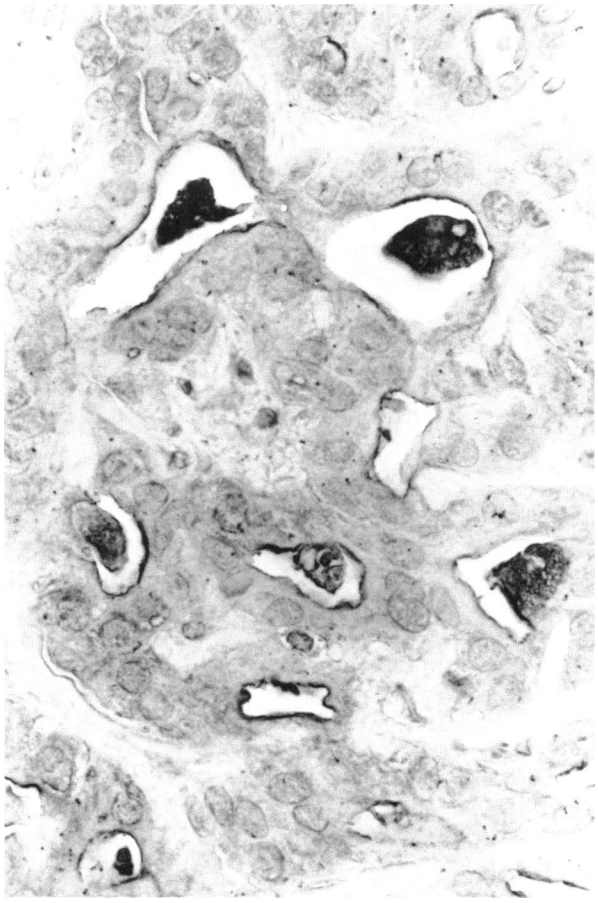

FIGURE 29. A-like antigen on the surface of induced pancreatic ductular carcinoma cells and in the luminal spaces. Immunoperoxidase–antiperoxidase with human anti-A serum. ×390

study examining the effect of ethanol on pancreatic carcinogenesis supported this point, since similar lesions, not found in any of the untreated controls in our colony, were induced with ethanol in BOP-treated hamsters (*32*). The latter finding excludes the role of a specific dietary nutrient in development of these lesions.

Now questions arise as to the nature of these lesions in hamsters. Are they reactive or neoplastic, as in rats? Can these lesions regress, as do some hyperplastic nodules in the liver? We believe they do regress in hamsters, but we do not yet have sufficient data to corroborate this. The current rate of progress in pancreatic carcinogenesis studies, however, should enable us to answer these questions soon.

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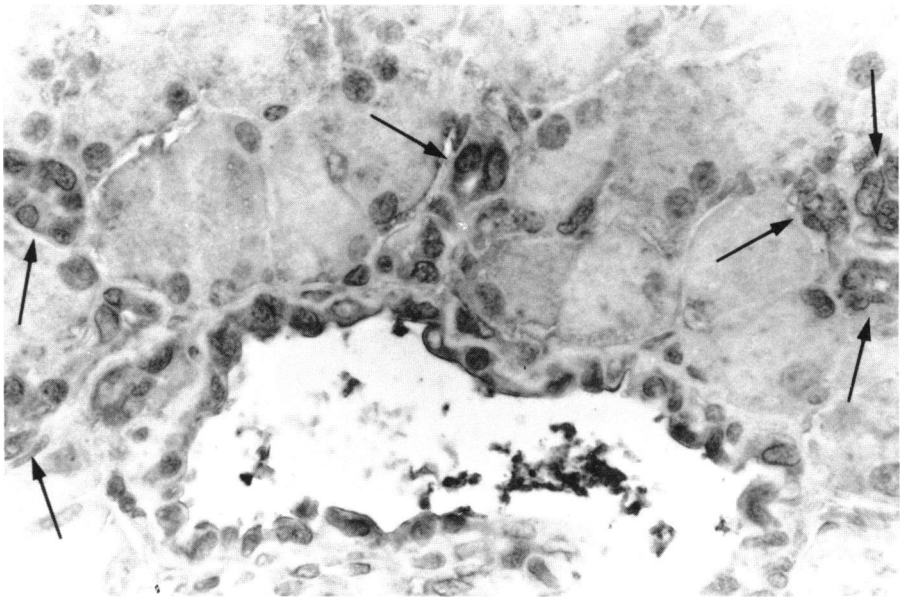

FIGURE 30. A-like antigen (dark material) in a large duct (top) and in several hyperplastic ductular cells (arrows) found during early stages of pancreatic carcinogenesis. Immunoperoxidase–antiperoxidase with human anti-A serum. ×390

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